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Massive fetal chylothorax successfully treated with postnatal talc pleurodesis: A case report and review of the literature

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ABSTRACT

Despite the rapid advances in fetal medicine and pediatric surgery, congenital chylothoraces have an associated mortality of 22–65% and an increased morbidity resulting from pulmonary hypoplasia, severe infections secondary to immune globulin deficiencies, protein malnutrition, and coagulopathy. While the mainstay of therapy is medical management, large volume chylothoraces often require surgical management. In both the prenatal and postnatal periods, the recommended management of congenital chylothoraces is still controversial. We present a case of a prenatally diagnosed large chylothorax associated with a cervical lymphatic malformation. In our patient, the chylothorax persisted despite optimal postnatal medical management with drainage by tube thoracostomy, TPN, and octreotide. Adjuvant therapies included sirolimus and sclerotherapy directed toward the treatment of the macrocystic lymphatic malformation. We report the first case of a persistent congenital chylothorax associated with a lymphatic malformation successfully treated with thoracoscopic talc pleurodesis and sclerotherapy.

Congenital chylothoraces are uncommon conditions, with an estimated occurrence of 1:10,000 to 1:15,000 pregnancies and an associated mortality of 22–65% [1,2]. Secondary causes of a congenital chylothorax include maternal or fetal infection, hydrops fetalis, fetomaternal hemorrhage, fetal anemia, congenital heart disease, congenital pulmonary lesions (congenital cystic adenomatoid malformations, bronchopulmonary sequestration), congenital diaphragmatic hernia, and lymphatic malformations [3]. In the postnatal patient, ongoing loss of lymphatic fluid via drainage of a high output chylothorax has been associated with risk of severe infection (observed in 33% of patients with congenital chylothorax), hypoproteinemia, hypogammaglobulinemia, and coagulopathy. An interdisciplinary medical and surgical approach is recommended due to the complexity of the disease and potential adverse sequelae [4,5]. We present the first reported case of a massive (>50 cc/kg/day output) congenital chylothorax associated with a lymphatic malformation of the neck that failed to respond to maximum medical management and was ultimately treated successfully with talc pleurodesis.

1. Case

A 30 year-old woman presented at 33 weeks gestation for routine follow up and was noted to have a fundal height greater than expected. Subsequent fetal US identified the presence of polyhydramnios, as well as bilateral moderate to large pleural effusions. Further antenatal evaluation with magnetic resonance imaging (MRI), demonstrated polyhydramnios, a large right pleural

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effusion with mediastinal shift, collapse of the right lung, and small volume ascites (Fig. 1). A complex, multiseptated, cervical cystic structure (3.2 cm × 1.1 cm × 2.3 cm) was also noted and appeared consistent with a macrocystic lymphatic malformation. Additional evaluation for sources of secondary pleural effusion demonstrated a normal fetal male karyotype, negative maternal screening for congenital infectious diseases (CMV, parvovirus, and toxoplasmosis), a negative maternal serum antibody test, and a fetal echocardiogram demonstrating normal cardiac structure and function.

Given the polyhydramnios and mediastinal shift resulting from the fetal hydrothorax, amnioreduction and ultrasound-guided right fetal thoracentesis was performed for both diagnostic and therapeutic purposes. Pleural fluid analysis demonstrated a cell count of 5187 cells/mL with 96% lymphocytes, consistent with the diagnosis of a chylothorax. Ultrasound performed the next day demonstrated rapid reaccumulation of moderate size bilateral chylothoraces. Given the rapid reaccumulation of bilateral chylothoraces, the decision was made to induce labor at 36 3/7 weeks gestational age (GA) in order to mitigate the risk of late term prenatal demise. US-guided right fetal thoracentesis was repeated, and vaginal delivery was subsequently induced. The baby boy was born at 36 3/7 weeks GA, weighing 2780 g.

Upon delivery, Apgar scores were 1, 4, and 7 at 1, 5, and 10 min, respectively. The baby was immediately noted to be apneic and to have poor tone; his breathing was assisted with bag mask ventilation followed by endotracheal intubation and initiation of inotropic support for concomitant hypotension. He was transferred to the neonatal intensive care unit (NICU), where a right-sided tube thoracostomy was performed, with drainage of 156 cc of serous fluid and radiographically confirmed resolution of his pleural effusion. The baby was initially managed conservatively, including being kept *nil per os* (NPO), using total parenteral nutrition (TPN), and replacing chest tube output 1:1 every 4 hours, with equal parts fresh frozen plasma (FFP) and 5% albumin. Over his first three days of life, the patient's chest tube output remained high (72–96 cc/kg/day), and an intravenous octreotide infusion was begun on day of life (DOL) #4, beginning at a rate of 1 mcg/kg/h, and advancing to a peak rate of 6 mcg/kg/h by DOL#8. In addition, on DOL#4 the patient underwent sclerotherapy to treat the macrocystic cervical lymphatic malformation (Fig. 2), and was started on sirolimus to assist with resolution of the lesion.

Despite continuation of medical therapy, by DOL#8, the patient's chest tube output remained elevated at 75 cc/kg/day, without response to initiation of either octreotide or sirolimus. With concern for newly diagnosed lymphopenia, as well as ongoing losses of protein, immunoglobulins, and coagulation factors, the decision was made to proceed with operative intervention, despite having not achieved the recommended octreotide rate of 10 mcg/kg/h [6]. On DOL#8, the patient underwent right-sided thoracoscopic talc pleurodesis. Intraoperative exploration was unsuccessful in identifying a discrete intrathoracic lesion responsible for the patient's continued chyle leak; therefore, pleurodesis was performed with aerosolized talc. The patient tolerated the procedure well; postoperatively, his chest tube output immediately and precipitously decreased to 2 cc/kg/day and remained negligible until his chest tube was discontinued. The sirolimus was continued until DOL#12, when it was discontinued due to supratherapeutic serum levels and concern for contributing immunosuppression in the setting of acquired bacteremia. Following treatment of the patient's bacteremia with intravenous antibiotics, the sirolimus was not

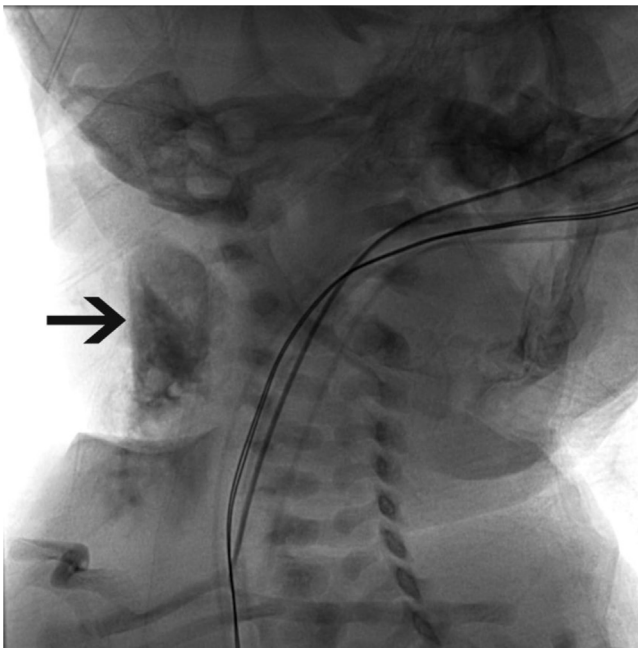

Fig. 2. AP fluoroscopy view of the baby's neck following injection of intralesional contrast and doxycycline into the right cervical macrocystic lymphatic malformation (black arrow).

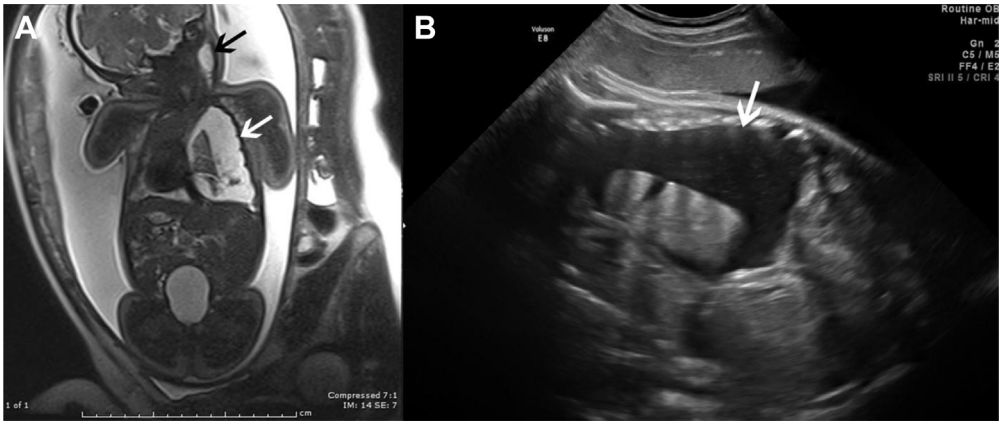

Fig. 1. (A) Coronal T2-weighted MRI image demonstrating a large right pleural effusion (white arrow) with mediastinal shift and a cystic lesion in the right neck consistent with a macrocystic lymphatic malformation (black arrow). (B) Comparison US long view of the fetal chest shows a large pleural effusion (white arrow) with flattening of the right hemidiaphragm.

restarted in the setting of consistently improving clinical status and negligible chest tube output.

On DOL#14/POD#7, the patient was started on enteral feeds with Enfaport (medium chain triglyceride formula), and TPN was discontinued three days later when the patient was tolerating full enteral feeds without a change in chest tube output. The patient was extubated on POD#8 to CPAP and gradually weaned to room air. The right chest tube was discontinued on DOL#29/POD#22. Patient was discharged home on DOL#35, tolerating full enteral feeds with Enfaport and 10% breast milk. At the time of manuscript submission, patient was 9 months old, meeting developmental milestones, on a diet of full breast milk, and was without evidence of redevelopment of his chylothorax on chest radiograph, despite cessation of sirolimus therapy on DOL#12 (Fig. 3).

2. Discussion

Management of congenital chylothoraces includes treatment of an underlying etiology, ligation of the thoracic duct, chemical pleurodesis, intrapleural maternal blood patch, mechanical pleurodesis, pleuroperitoneal shunt, and pleurectomy [1,4,7,8]. Medical management focuses upon maneuvers which minimize chyle production, such as keeping the patient NPO, nutritional support with TPN, enteral feeds with medium chain triglycerides, and intravenous octreotide [9]. However, in patients whose tube thoracostomy output remains high despite maximal medical therapy, consideration of early operative intervention, including talc pleurodesis, may minimize complications and reduce overall length of stay [4].

While previous studies recommend consideration of operative intervention if chylous drainage remains >15 cc/kg/day after 7 days of maximal medical management, recent studies have recommended that output >50 cc/kg/day (defined as a 'massive' chylothorax) despite maximal medical therapy for 3 days should be an indication to proceed with early surgical intervention [7,10]. A recent study in 34 adults with non-traumatic chylothoraces demonstrated that thoracic duct embolization was successful in over 60% of patients with an abnormal lymphangiogram; however, lymphatic channel embolization can be technically challenging in the neonatal population [11]. More commonly, mechanical pleurodesis, pleurectomy, or chemical pleurodesis have been the mainstays of treatment for congenital chylothoraces. Given concern for the risk of blood loss associated with pleurectomy in neonatal patients, chemical pleurodesis should be considered when imaging fails to demonstrate an etiology amenable to thoracic duct ligation or embolization. Congenital chylothoraces that remain unresponsive to mechanical or chemical pleurodesis are treated with either pleuroperitoneal shunts or pleurectomy; however, there is concern as to whether the neonatal peritoneal cavity is able to accommodate and absorb the volumes of chyle that can be produced by massive congenital chylothoraces [4].

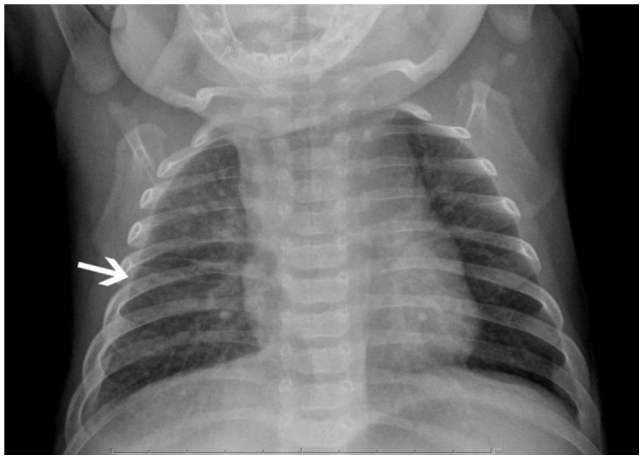

Fig. 3. AP radiograph of the chest at the time of discharge demonstrates almost complete resolution of bilateral pleural effusions with only trace residual effusion on the right (white arrow).

In the pediatric population, there is ongoing debate regarding the optimal agent for chemical pleurodesis. While a meta-analysis in adults demonstrated over 90% success rate with the use of povidone-iodine to treat pleural effusions, it's use in the pediatric population has been limited due to concerns regarding an increased risk of renal failure, acidosis, acute respiratory distress syndrome, and associated mortality with its use in pediatric patients [4,12,13]. Several recent case reports document successful treatment of fetal pleural effusions with in-utero pleurodesis using OK-432, a lyophilized version of low virulence Group A *Streptococcus*, specifically when pleuroamniotic shunting has failed; however, OK-432 is no longer available in the United States [14–17]. Alternatively, chemical pleurodesis with talc is considered the most effective therapy for adults with malignant pleural effusions or spontaneous pneumothoraces [18]. After case reports questioned an increased risk of acute respiratory distress syndrome (ARDS) following talc pleurodesis, a multicenter, randomized trial failed to demonstrate an association between talc pleurodesis and ARDS in adults [18]; furthermore, two prospective, randomized studies examining the effectiveness of pleurodesis with talc versus povidone-iodine demonstrated equal efficacy, without significant difference in adverse events (recurrence, ARDS, or hypotension) [12,19]. We were unable to find a single case report, let alone a prospective trial, examining the impact of talc pleurodesis on the natural history of congenital chylothoraces.

Our patient underwent serial antenatal thoracentesis, followed by postnatal tube thoracostomy and sclerotherapy directed at treatment of his underlying macrocystic lymphatic malformation. Postnatally, our patient was initially managed medically, receiving the full benefit of a multidisciplinary team of neonatalogists, pediatric surgeons, hematologist-oncologists, and interventional radiologists; however, after 3 days of maximal medical management, as well as sclerotherapy and the initiation of sirolimus targeted at treatment of his cervical cystic lymphatic malformation, his chest tube output remained very high (75 cc/kg/day) [20]. Sirolimus, also known as rapamycin, is an inhibitor of the mammalian target of rapamycin (mTOR). In a number of vascular anomalies, specifically those demonstrating atypical lymphatic pathology, mTOR expression is upregulated [21]. Case reports have documented the effective treatment of chylothoraces associated with lymphatic malformation using sirolimus [21–23]. As the average time to response in these cases was 25 days, given time, it is possible that our patient's chylothorax would have resolved with medical management, given time. However, our patient's ongoing chest tube output remained very high (75 cc/kg/day) and, faced with rapid clinical decompensation, an alternative therapeutic approach was required. In accordance with the recommendations of Cleveland et al. (2009), we felt the patient would benefit from early surgical intervention in order to minimize the risks of ongoing chylous losses, including his known lymphopenia, and the risk of severe infection, coagulopathy, electrolyte abnormalities, and hypoproteinemia. Given the large literature base in adult populations, the lack of reported adverse events with talc versus povidone-iodine, and the lack of access to OK-432 in the United States, we chose to utilize talc pleurodesis in the treatment of our patient; we observed near immediate resolution of the patient's congenital chylothorax, without evidence of recurrence or adverse event four months postoperatively.

3. Conclusion

In the setting of a high volume congenital chylothorax, antenatal intervention with either serial thoracentesis or pleuroamniotic shunting should be pursued to minimize the associated morbidity and mortality due to pulmonary hypoplasia. Chemical pleurodesis has been demonstrated to be safe and effective for neonatal patients with chylothoraces unresponsive to medical management; however, the specific agent of choice remains undefined. We have presented a case of a patient with a cervical lymphatic malformation and massive congenital chylothorax, which was unresponsive to medical management and was treated very successfully with thoracoscopic talc pleurodesis. In the setting of a large volume congenital chylothorax resistant to medical management, talc pleurodesis should be considered early given the risk of hypoproteinemia, hypogammaglobulinemia, leukopenia, coagulopathy, volume shifts and electrolyte disturbances, and potentially fatal infections risked by ongoing losses of lymphatic fluid.

Conflicts of interest and source of funding

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